

PRESCRIBING INFORMATION

Pr JAMP Chlorthalidone

Chlorthalidone Tablets USP

12.5 mg, 25 mg and 50 mg

Diuretic - Antihypertensive

**JAMP Pharma Corporation
1310, rue Nobel
Boucherville, Quebec
J4B 5H3**

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THERAPEUTIC CLASSIFICATION

Diuretic - Antihypertensive

ACTIONS AND CLINICAL PHARMACOLOGY

Chlorthalidone inhibits reabsorption of sodium and chloride in the distal renal tubule thus promoting water loss. The higher urine volume increases potassium loss. Little information is available on the absorption of the drug. Its long elimination half-life and clinical experience place it as a long- acting thiazide derivative. This may not be important clinically because the biological effects of thiazides particularly as antihypertensives may be prolonged compared to their elimination rate.

The longer acting agents appear to cause increased potassium loss.

Although a mild diuretic, its combination with loop diuretics is particularly potent because the latter presents much more sodium chloride to the distal tubule.

The blood pressure lowering effects are initially due to volume reduction but the persisting effect includes other undetermined mechanisms that reduce peripheral resistance. A high salt intake reverses its antihypertensive effect.

The major portion of an absorbed dose of chlorthalidone is excreted by the kidneys with an elimination half-life averaging 50 hours. Metabolism and hepatic excretion into the bile constitute a minor way of elimination. Within 120 hours, about 70% of the dose is excreted in the urine and in the feces, mainly in an unchanged form.

INDICATIONS AND CLINICAL USE

For the treatment of hypertension. It may be used alone or in association with other antihypertensive agents.

Chlorthalidone is also indicated for adjunctive therapy of edema associated with: renal disease; congestive heart failure of mild to moderate degree (functional class II, III), when glomerular filtration rate is greater than 30 mL/min; ascites due to cirrhosis of the liver in stable patients; estrogen therapy; corticosteroid therapy.

CONTRAINDICATIONS

Anuria, severe renal failure (creatinine clearance lower than 30 mL/min), severe hepatic failure, refractory hypokalemia or conditions involving enhanced potassium loss, hyponatremia, hypercalcemia, symptomatic hyperuricemia (history of gout or uric acid calculi).

Pregnancy: See PRECAUTIONS, Pregnancy.

Hypersensitivity or suspected hypersensitivity to chlorthalidone and other sulfonamide derivatives or their excipients.

WARNINGS

Should be used with caution in patients with renal disease or with impaired hepatic function (see Contraindications and Precautions). Because of the possibility of progression of renal damage, periodic determination of the BUN and serum creatinine are indicated. Should there be an elevation of either parameter, treatment should be discontinued. Like thiazides, chlorthalidone

may lose its diuretic efficacy when glomerular filtration rate drops below 30 mL/min, a point at which treatment with loop diuretics may be more appropriate.

Electrolytes

As with thiazide diuretics, kaluresis induced by chlorthalidone is dose dependent, and there is inter-individual variability in magnitude. With 25 mg/day, serum potassium concentration decreases average 0.5 mmol/L. If chronic treatment is contemplated, serum potassium concentrations should be determined initially, and then 3 to 4 weeks later. If, thereafter, potassium balance is not disturbed further, concentrations should be assessed every 4 to 6 months. Conditions that may alter potassium balance (especially in the presence of brisk diuresis) include: vomiting, diarrhea, malnutrition, change in renal function (e.g., nephrosis), liver cirrhosis, hyperaldosteronism, or concomitant use of corticosteroids or ACTH.

Titrated co-administration of an oral potassium salt (e.g., KCl) may be considered in patients: receiving digitalis; exhibiting signs of coronary heart disease, unless they are also receiving an ACE inhibitor; on high doses of a beta-adrenergic agonist; whose plasma potassium concentrations are less than 3.0 mmol/L.

If oral potassium preparations are not tolerated, chlorthalidone may be combined with a potassium-sparing diuretic (e.g., triamterene).

Patients receiving thiazides and their analogues should be carefully observed for clinical signs of fluid or electrolyte imbalance. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or

cramps, muscular fatigue, gastrointestinal disturbances, hypotension, oliguria, tachycardia, and cardiac arrhythmias or corresponding ECG changes.

In all combination treatment regimens, maintenance or normalization of the potassium balance should be closely checked. If hypokalemia is accompanied by clinical signs (e.g., muscular weakness, paresis and ECG alteration), chlorthalidone should be discontinued.

Combined treatment consisting of chlorthalidone and a potassium salt or a potassium-sparing diuretic must be avoided in patients also receiving ACE inhibitors.

Close monitoring of serum electrolytes is indicated particularly in the elderly, in digitalized patients, in patients vomiting excessively or receiving parenteral fluids, patients with ascites due to liver cirrhosis, and in patients with edema due to nephrotic syndrome. For the latter condition, chlorthalidone should be used only under close control in normokalemic patients with no signs of volume depletion or severe hypoalbuminemia.

Excessively strict low-salt diets should be avoided. Hyponatremia, accompanied by neurological symptoms (nausea, debility, progressive disorientation, apathy), has been observed in isolated cases.

Should hypochloremic alkalosis or hyponatremia occur, consider appropriate therapy. Water restriction rather than actual salt replacement may be considered appropriate treatment of any chloride deficit except in rare instances when hyponatremia is life threatening, then appropriate salt replacement is the therapy of choice.

Patients receiving relatively high doses of thiazides or their analogues may develop hypomagnesemia accompanied by such signs and symptoms as nervousness, muscle spasm, and cardiac arrhythmias.

Thiazides may decrease protein bound iodine levels without signs of thyroid disturbance.

Pathological changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen. Discontinue thiazides and their analogues before carrying out tests for parathyroid function.

Calcium excretion is decreased by thiazide diuretics.

Metabolic Effects

Chlorthalidone may raise the serum uric acid level, but attacks of gout (in predisposed patients) are rarely observed during chronic treatment. In cases where prolonged and significant elevation of blood uric acid concentrations is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Small and partially reversible increases in plasma concentrations of total cholesterol, triglycerides, or low-density lipoprotein cholesterol were reported in patients during long-term treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is equivocal.

Chlorthalidone should not be used as a first-line drug for long-term treatment in patients with overt diabetes mellitus or in patients with hypercholesterolemia. If chlorthalidone must be used, serum lipids should be regularly monitored. If there is a rise in lipid levels, withdrawal of chlorthalidone should be considered.

Although glucose tolerance may be adversely affected, diabetes mellitus very seldom occurs under treatment.

Patients with Special Diseases and Conditions

In patients with impaired hepatic function or progressive liver disease, caution should be exercised since even minor alterations in fluid and electrolyte balance or of serum ammonia may precipitate hepatic coma.

Treatment with thiazide diuretics should be initiated cautiously in postsympathectomy patients since the antihypertensive effects may be enhanced.

A cautious dosage schedule should be adopted in patients with severe coronary or cerebral atherosclerosis.

General

The antihypertensive effect of ACE inhibitors is potentiated in the presence of agents that increase plasma renin activity (diuretics). A cautious dosage schedule should therefore be adopted when an ACE inhibitor is added to a diuretic agent.

Occupational Hazards

Because dizziness and impaired patient reaction time are possible side effects of chlorthalidone, especially at the start of therapy, patients should be warned about the possible hazards of operating machines or driving motor vehicles.

Pregnancy

Chlorthalidone, like other diuretics, can cause placental hypoperfusion. Since they do not prevent or alter the course of EPH (edema, proteinuria, hypertension) -gestosis (pre-eclampsia), these drugs must not be used to treat hypertension in pregnant women. The use of chlorthalidone for other indications (e.g., heart disease) in pregnancy should be avoided, particularly in the first trimester, unless the potential benefits outweigh the possible risks (e.g., when there are no safer alternatives).

As thiazides increase blood uric acid concentration, levels should be taken before and during pregnancy but their value in assessing the onset of toxemia may still be lost.

Chlorthalidone crosses the placental barrier. Levels in fetal whole blood were about 15% of those found in the maternal blood of mothers receiving 50 mg chlorthalidone daily pre-and postpartum. Concentration in amniotic fluid is approximately 4% of maternal blood levels.

Lactation

Chlorthalidone appears in breast milk, attaining concentrations of approximately 4% of maternal blood levels. Therefore use in nursing mothers should be avoided.

Drug Interactions

Antihypertensive Agents: Diuretics potentiate the action of curare derivatives and antihypertensive agents (e.g., guanethidine, methyldopa, beta-blockers, vasodilators, calcium antagonists, ACE inhibitors).

Postural hypotension may occur and may be potentiated by alcohol, anesthetics, sedatives, barbiturates or narcotics.

Digitalis: Thiazide-induced hypokalemia or hypomagnesemia may increase the likelihood of digitalis-induced cardiac arrhythmias (see also Precautions).

Corticosteroids: The hypokalemic effects of diuretics may be increased by corticosteroids, ACTH and amphotericin.

Insulin and Oral Antidiabetic Agents: It may be necessary to adjust the dosage of insulin or oral antidiabetic agents in response to changes in glucose tolerance that chlorthalidone may produce (see PRECAUTIONS, Metabolic Effects).

NSAIDs: Concomitant administration of certain NSAIDs (e.g., indomethacin) may weaken the diuretic and antihypertensive activity of thiazides, and there have been isolated reports of a deterioration of renal function in predisposed patients.

Curare Derivatives and Ganglionic Blocking Agents: Thiazides may increase responsiveness to curare derivatives and ganglionic blocking agents.

Allopurinol: Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine: Co-administration of thiazide diuretics may increase the risk of adverse effects from amantadine.

Antineoplastic Agents (e.g., cyclophosphamide, methotrexate): Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance the myelosuppressive effects.

Anticholinergics (e.g., atropine, biperiden): The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents, apparently due to a decrease in gastrointestinal motility and rate of gastric emptying.

Lithium: Diuretics enhance the cardiotoxic (manifested in ECG changes) and neurotoxic (manifested by ataxia, confusion, and mental disorientation) effects of lithium and these drugs should not be administered concurrently. In those rare instances when these drugs must be given together, patients should be observed closely for signs and symptoms of lithium toxicity. Close monitoring of serum electrolytes and lithium concentrations and maintenance of adequate fluid, potassium and sodium intake are also necessary.

Cholestyramine: Absorption of thiazide diuretics is decreased by cholestyramine, therefore a decrease in pharmacological effect may be expected.

Vitamin D: Concomitant use of thiazide diuretics may decrease urinary excretion of calcium, and co-administration of Vitamin D may potentiate the increase in serum calcium.

Cyclosporin: Concomitant treatment with diuretics may increase the risk of hyperuricemia and gout-type complications.

Calcium Salts: Concomitant use of thiazide-type diuretics may cause hypercalcemia by increasing tubular calcium reabsorption.

Diazoxide: Thiazide diuretics may enhance the hyperglycemic effect of diazoxide.

ADVERSE EFFECTS

Frequency estimates are as follows: Frequent: >10%, Occasional: 1 to 10%, Rare: 0.001 to 1% and Isolated Cases: <0.001%.

Electrolytes and Metabolic Disorders: Frequent: mainly at higher doses, hypokalemia, hyperuricemia, and rise in blood lipids. Occasional: hyponatremia, hypomagnesemia, and hyperglycemia. Rare: hypercalcemia, glycosuria, worsening of diabetic metabolic state, and gout. Isolated cases: hypochloremic alkalosis.

Dermatology: Occasional: urticaria and other forms of skin rash. Rare: photosensitization.

Liver: Rare: Intrahepatic cholestasis or jaundice.

Cardiovascular: Occasional: postural hypotension, which may be aggravated by alcohol, anesthetics or sedatives. Rare: cardiac arrhythmias.

CNS: Occasional: dizziness, slow mentation and decreased reaction time (see PRECAUTIONS). Rare: paresthesia, headache.

Gastrointestinal: Occasional: loss of appetite and minor gastrointestinal distress. Rare: mild nausea and vomiting, gastric pain, constipation, and diarrhea. Isolated cases: pancreatitis.

Hematology: Rare: thrombocytopenia, leukopenia, agranulocytosis and eosinophilia, aplastic anemia.

Miscellaneous: Occasional: impotence. Rare: disturbances of vision. Isolated cases: idiosyncratic pulmonary edema (respiratory disorders). Allergic interstitial nephritis and vasculitis.

SYMPTOMS AND TREATMENT OVERDOSAGE

Symptoms: Symptoms of chlorthalidone overdose may include nausea, weakness, dizziness, somnolence, hypovolemia, hypotension, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasm.

Treatment: There is no specific antidote. To reduce absorption, induce vomiting or gastric lavage and administer activated charcoal. Intravenous dextrose-saline and potassium chloride may be given, if necessary, with due caution.

DOSAGE AND ADMINISTRATION

Therapy should be initiated with the lowest possible dose, and be titrated thereafter to gain maximum therapeutic benefit while keeping side effects to a minimum (e.g., determine the minimum effective maintenance dose for each patient). A single dose daily or every other day given in the morning with food is recommended.

Hypertension: Usual adult dose is 25 to 50 mg daily. The clinically useful dosage range is 12.5 to 50 mg daily. Doses greater than 50 mg per day increase metabolic complications and are rarely

of therapeutic benefit. For a given dose, the full effect is reached after 3 to 4 weeks. If the decrease in blood pressure obtained using doses of 25 or 50 mg/day proves inadequate, combined treatment with other antihypertensive drugs from a different class (such as beta-blockers or ACE inhibitors) is recommended. When adding another hypertensive drug (such as an ACE inhibitor), the dose of chlorthalidone is to be reduced.

Edema of Specific Origin (see INDICATIONS): The lowest effective dose is to be identified by titration. Maintenance doses should not exceed 50 mg/day and should be administered over limited periods only. The dosage should be individually adapted to the clinical picture and patient's response. For long-term therapy, the lowest possible dosage sufficient to maintain an optimal effect should be employed; this applies particularly to elderly patients.

The therapeutic effect of chlorthalidone occurs even without salt restriction and is well sustained during continued use.

CLINICAL TRIALS**Comparative Bioavailability Study**

A randomized, two-way crossover, single 1 x 50 mg dose bioequivalence study of ^{Pr}JAMP Chlorthalidone (Chlorthalidone Tablets USP) 50 mg (JAMP Pharma Corporation) and ^{Pr}CHLORTHALIDONE (Chlortalidone Tablets BP) 50mg (AA Pharma Inc., Canada) was conducted in healthy, adult, male and female Asian subjects under fasting conditions. A summary of the comparative bioavailability data from the 30 subjects who completed the study is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Chlorthalidone (1 x 50 mg) Geometric Mean Arithmetic Mean (%CV)				
Parameter ¹	TEST ²	REFERENCE ³	% Ratio of Geometric Means	90 % Confidence Interval
AUC ₀₋₇₂ ⁴ (ng•h/mL)	5879.15 6222.27 (31.74)	5812.49 6123.78 (30.99)	101.1	92.8 – 110.3
C _{max} (ng/mL)	231.23 251.35 (38.49)	223.74 236.86 (32.76)	103.3	94.3 - 113.3
T _{max} ⁵ (h)	3.50 (1.00 - 9.00)	2.68 (1.00 - 6.02)	NA	NA

¹ Due to the long elimination half-life of chlorthalidone, AUC₁ and T_{1/2} could not be accurately calculated from the data obtained in this study.

² ^{Pr}JAMP Chlorthalidone (Chlorthalidone Tablets USP) 50 mg (JAMP Pharma Corporation)

³ ^{Pr}CHLORTHALIDONE (Chlortalidone Tablets BP) 50mg (AA Pharma Inc., Canada)

⁴N = 29 subjects

⁵ Expressed as the median (range) only

AVAILABILITY OF DOSAGE FORMS

12.5 mg JAMP Chlorthalidone tablets are light yellow, round, bevel edged, unscored tablets debossed with "C" on one side and plain on the other side. Available in bottles of 100.

25 mg JAMP Chlorthalidone tablets are light yellow, round, bevel edged, unscored tablets debossed with "C" on one side and "25" on the other side. Available in bottles of 100.

50 mg JAMP Chlorthalidone tablets are light yellow, round, bevel edged, scored tablets debossed with "50" to the right of the score and "C" on the other side. Available in bottles of 100.

Composition

In addition to chlorthalidone, each tablet contains the non-medicinal ingredients microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, D&C yellow #10 and FD&C yellow #6.

Stability and Storage Recommendations

Store at room temperature (15 to 30°C).